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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/613,272	MAMULA, MARK J.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *6-9,15,16,23 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-5,10-14,17-22 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of the invention of Group I in the reply filed on September 11, 2006 is acknowledged. Acknowledgement is also made of applicants election of the species of "tumor antigens" in the same reply. Applicant state that claims 1-5, 10-14, 17-22 and 25-29 read on the elected species, however, claim 29 is not part of the elected Group I.

Claims 1-29 are pending. Claim 29, drawn to a non-elected invention, is withdrawn form consideration. Claims 6-9, 15, 16, 23 and 24, drawn to non-elected species are also withdrawn from consideration. Claims 1-5, 10-14, 17-22 and 25-28 are examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10, 17 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10, 17 and 19 recite an "aspartic acid residue" or "asparagine residue" comprises an amino acid sequence. It is unclear how a single amino acid residue can comprise an amino acid sequence.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 10-14, 17-22 and 25-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A)As drawn to a method of enhancing the immune response of a patient

The specification teaches that tumor cells treated with adenosine dialdehyde for isoaspartic acid residues thereon, and that administration of said tumor cells to mice bearing the same unmodified tumor results in the generation of CTL against the modified tumor cells which cross-react with unmodified tumor cells. The instant claims encompass the generation of an immune response, compositions comprising tumor antigen-modified peptides, wherein the modification is an isoaspartic acid residue, and vaccines and compositions comprising fragments of modified tumor antigens comprising isoaspartic acid residues effective to enhance the immune response against a naturally occurring tumor in a patient.. The claims encompass the any time of tumor tissue and any fragment of a tumor antigen. it is well recognized in the art that clinical results on patients do not reflect the results of animal models. For example Schultze et al (Trends in Immunology, 2004, Vol. 25, pp 659-664) teach that encouraging animal model studies lead to clinical trails, but that the general outcomes of these trials are disappointing, citing a discrepancy between the outcome of pre-clinical models and the outcome of the human situation. Bodey et al, (Anticancer Research, 2000, Vol. 20, pp. 2665-2676) teach that the animal models often produce highly encouraging results but that the resulting response in humans is disappointing. As a specific example it is noted that in 1995 Addissson et al (PNAS, Vol. 92, pp. 8522-8526) taught that intratumor injection of an adenovirus encoding Il-2 induces regression and immunity in a breast cancer animal model. However, this pre-clinical outcome has not translated into a reliable treatment for breast cancer patients as of the present. Thus the results of the studies on transplanted tumors in mice do not provide a reliable nexus for the treatment of a naturally arising tumor in a patient.

Claims 11-14, 17-22, 25-28 are drawn to methods of enhancing the immune response of a patient relative to the normal immune response comprising administering to a said patient a tumor antigen comprising the isoaspartic acid residues or a fragment of said tumor antigen comprising the isoaspartic acid residues Le Fur et al (PNAS, 1997, Vol. 94, pp. 7561-7565) teach that results pertaining to the rejection of transplanted tissue differs from raising an immune response in a patient against a primary tumor in its natural place (page 7564, second column, lines 13-15 in the third full paragraph). Le Fur et al conclude that many practical issues need to be resolved before an effective peptide-antigen tumor vaccine is obtained from peptides identified by T cell recognition or predicted by over expressed RNA isoforms in tumors (page 7565 last paragraph).

(B) As drawn to a vaccine

Claims 26-28 require a vaccine. The art teaches that a vaccine must be prophylactic (Stedman's Medical dictionary, 2000, lines 1-3). The specification does not provide any teachings of the prophylaxis of cancer, how to determine the individuals who will develop a particular cancer, nor how to effectively prevent said particular cancer type before occurrence. Thus, one of skill in the art would not be able to use the composition of the invention as a vaccine without undertaking to determine how to select for individuals which will develop a particular cancer type before the said cancer occurs in the individual.

The abstract of Wheeler (Salud p'ublica de M'exico, (1997 Jul-Aug) 39 (4) 283-7) teaches that a cancer vaccine against human papillomavirus for the treatment of cervical cancer requires not only the activation of antigens and overcoming the host response, but the generation of high levels of T and B memory cells; and the persistence of antigens. The instant specification has not provided any teachings regarding the persistence of the tumor antigens in an individual who has yet to develop a specific type of cancer. Further, Efferson et al (Anticancer research, 2005, Vol. 25, pp. 715-724) teach that efficient induction of memory cells is hindered by the lack of information about the relationship between TCR stimulation and the cytokines required for Ag-specific memory CD8+ cells and proliferation and survival. It is noted that the instant specification has not provided any evidence that adequate levels of T and B memory cells would persist in an immunized individual who has not developed a cancer, and Efferson et al is clearly discussing a need in the art as of 2005, three years after the prioirty date of the instant

specification, therefore the enablement for how to generate adequate memory T and B cells can not be provided from the general knowledge of in the art. Bachman et al (Journal of Immunology, 2005, Vol. 175, pp. 4677-4685) teach that memory T cells are not a homogeneous population and can be divided into central memory T cells with a substantial capacity for recall proliferation and effector memory T cells with limited recall proliferation capacity. Bachman et al teach that the protective capacity of the different subpopulations of memory T cells vary, and the generation of the subpopulations is influenced by the nature and route of immune challenge. These references serve to demonstrate that the prior art is not mature with respect to how to elicit an effective prophylactic memory cell response that will persist in an individual not harboring a tumor cells and which would function to protect said individual from tumor cell development. Because the specification does not address the issues in the post-filing date art regarding how to elicit an effective memory cell response from the administration of the claimed compositions, and no objective evidence or working examples have been provided, one of skill in the art would be subject to undue experimentation in order to make and use the claimed composition as a vaccine.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5 and 10are rejected under 35 U.S.C. 102(b) as being anticipated by Ramakrishna and Shinitzky (Cancer Immunol Immunother, 1991, Vol. 33, pp. 1-8) as evidenced by Desrivieres et al (JBC, 1997, Vol. 272, pp. 2470-2476).

claim 1 is drawn to a method for enhancing the immune response of a patient relative to the normal immune response comprising growing cells containing a tumor antigen under

conditions wherein an aspartic acid residue or an asparagine residue in said tumor antigen is converted to an isoaspartic acid residue, and administering said cells or isolated isoaspartic acid residues to the patient to enhance the immune response. Claim 2 embodies the method of claim 1 wherein the growing step comprises exposing said cells containing the tumor antigen to adenosine dialdehyde. Claim 5 embodies the method of claim 1 wherein said tumor antigen s selected from a group including CDK-4. Claim 10 embodies the method of claim 1 wherein said aspartic acid residue or asparagine reside comprises an amino acid sequence selected from the group consisting of Asn-Gly, Asn-Ser, Asp-Gly and Asp-Ser.

Ramakrishna and Shinitzky disclose the modification of El4 cells by incubation in ox-dAdo at room temperature (page 2, first column, under the heading of Modification 1) which fulfills the specific embodiment of claim 2. Ramakrishna and Shinitzky disclose that the modified EL4 tumor cells induced CTL against non-modified EL4 cells (page 7, first full paragraph). Desrivieres et al disclose that EL4 cells have Cyclin 4 activity (page 2472, second column, under the heading "differential Inhibition of G1 Cyclin-CDK Complexes by PMA and Concanavalin"), which fulfills the specific embodiment of claim 5 as directed to CDK-4.

Claims 26-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Heavner et al (U.S. 5,298,490) as evidenced by Azorsa et al (Blood, 1991, Vol. 78, pp. 280-284).

Claim 26 is drawn in part to a fragment of a protein selected from a group including tumor antigens, wherein said fragment comprises an isoaspartic acid residue, and a pharmaceutically acceptable carrier. Claim 27 embodies the vaccine of claim 26 wherein the pharmaceutically acceptable carrier is selected from a group including a solid carrier material. Claim 28 embodies the vaccine of claim 26 wherein said pharmaceutically acceptable carrier is selected from a group including sugar, starch and water.

Heavner et al disclose pharmaceutical compositions comprising the peptides of claim 1 (claim 20) which include a beta-Asp residue at position "Y". Beta-Asp is synonymous with isoaspartic acid. Heavner et al disclose the oral administration of said peptides as a preferred embodiment (column 8, lines 19-21, and column 9, lines 21-30) and a pharmaceutical composition comprising a solid carrier material such as starches and sugars, in addition to a liquid carrier such as water (column 9, lines 31-39). Heavner et al disclose that said peptides

increase T cell helper activity (column 4, lines 29-44). Heavner et al do not disclose the peptides as fragments of a tumor antigen. Azorsa et al disclose the CD63 protein (page 282) which comprises the peptide of Heavner et al prior to domination to produce the isoaspartic acid residue (see attached alignment). Azorsa et al disclose that CD63 is identical to the stage-specific melanoma associated antigen, ME491 (page 282, second column, lines 14-17). Thus the disclosure of the terapeptides comprising the isoaspartic acid residue of Heavner et al meet the specific embodiment of a fragment of a tumor antigen, and satisfy the limitation of claim 26 to the extent that said claim encompasses a pharmaceutical composition.

All claims are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A Canella, Ph.D.
11/26/2006

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